

Attorney Docket No.: RCK0017US.NP
Inventors: Fuchs et al.
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REMARKS

Claims 1-5 and 7-16 are pending. Claim 1-5 and 7-16 have been rejected. Claim 2-5 and 9-16 have been canceled. No new matter has been added. Applicants are respectfully requesting reconsideration of the restriction requirement in view of the following remarks.

I. Withdrawn Objections/Rejections

Applicants acknowledge the withdrawal of the rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,665,557.

II. Rejection of Claims Under 35 U.S.C. §102

Claims 2-5 remain rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,665,557 as evidenced by Schrieber et al. ((2009) *Haematologica* 94:1493-1501) and further evidenced by Akashi et al. ((2003) *Blood* 101:383-390). The Examiner suggests that the '557 patent teaches hematopoietic cells, which fulfill the definition of self-renewing, multipotent, and slow-cycling that were selected by expression of CD34. It is suggested that in so far as Schrieber et al. and Akashi respectively teach that hematopoietic stem cells express alpha-6-integrin and transcription factor 3, expression of these markers would be inherent in the cells of the '557 patent.

Applicants respectfully disagree. However, in the interest of placing the application in condition for allowance, Applicants have canceled claims 2-5 without prejudice, reserving the right to file continuing applications on the canceled subject matter. In light of

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this amendment, it is respectfully requested that this rejection be reconsidered and withdrawn.

Claims 2-5 and 7-16 have been rejected under 35 U.S.C. 102(a) as being anticipated by Tumbar et al. ((2004, available on-line December 11, 2003) *Science* 303:359-363). It is suggested that Tumbar et al. teach the cells of claims 2-5 and 6-16 as well as the method of claim 7 thereby anticipating the claims. Applicants respectfully traverse this rejection.

At the outset, while the Examiner makes specific reference to passages in Tumbar et al. which purportedly anticipate the subject matter of claims 2-5, 7, and 9-16, the Examiner has not identified the pertinence of this reference as it relates to claim 8. MPEP Appendix R, §1.104(c)(2).

In any event, the present application is the U.S. National Phase of, and claims benefit of priority from, PCT/US04/37925, filed November 12, 2004. Tumbar et al. is Applicants' own publication published in Volume 303 of *Science*, which was available to the public on December 11, 2003. As such, Tumbar et al. published less than a year before the effective filing date of the instant application, i.e., November 12, 2004, the filing date of priority application PCT/US04/37925. Applicants' disclosure of his or her own work within the year before the application filing date cannot be used against him or her as prior art. *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982). Accordingly, Applicants submit herewith a 1.132 Declaration by Elaine Fuchs, Tudorita Tumbar, Cedrick Blanpain and William E. Lowry indicating that while the assistance of the co-authors of Tumbar et al. was a tremendous aid to obtaining the data

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disclosed in this publication, Geraldine Guasch, Valentina Greco, and Michael Rendl did not directly contribute to the conceptualization of the present invention. Because Tumbar et al. is not by another nor was it published more than twelve months prior to the present application, it is an improper prior art reference under 35 U.S.C. 102(a). Accordingly, it is respectfully requested that this rejection be reconsidered and withdrawn.

III. Rejection of Claims Under 35 U.S.C. §103

Claims 1-5 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Tumbar et al. when taken with U.S. Patent No. 5,665,557.

Applicants respectfully traverse this rejection. As indicated above, Tumbar et al. is not by another nor was it published more than twelve months prior to the present application. Therefore, Tumbar et al. is an improper prior art reference under 35 U.S.C. 102(a) and therefore is disqualified as a prior art reference under 35 U.S.C. 103(a). In so far as the secondary reference alone fails to teach or suggest the claimed invention, this rejection cannot be sustained. It is therefore respectfully requested that this rejection be withdrawn.

Claims 7 and 9 remain rejected under 35 U.S.C. 103(a) s being unpatentable over U.S. Patent No. 5,639,618 when taken with Strathdee et al. ((1999) *Gene* 229:21-29) and Bohl et al. ((1997) *Nat. Med.* 3:229-305) when taken with Mahmud ((2001) *Blood* 97:3061-3068) and U.S. Patent 6,485,971.

Claims 8 and 10-14 remain rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,639,618 when taken with Strathdee et al. and Bohl et al. when taken

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with Mahmud and U.S. Patent 6,485,971 as applied to claims 7 and 9, and further in view of U.S. Patent No. 5,665,557.

Likewise, claims 15-16 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Strathdee et al. and Bohl, et al. when taken with Mahmud et al. and U.S. Patent No. 6,485,971 and U.S. Patent No. 5,665,557 as applied to claims 7-14 above, and further in view of U.S. Patent No. 5,861,315.

Applicants respectfully disagree with these rejections. As Applicants have pointed out in the previous response, there are considerable differences between the cells of the instant invention and the combined teachings of the cited references. However, in the interest of placing the application in condition for allowance, Applicants have canceled claims 9-16 without prejudice, reserving the right to file continuing applications on the canceled subject matter.

Turning to the methods of claims 7 and 8, Applicants respectfully point out that the rejections of record do not identify how every limitation of the claimed invention is found in the references of record. To support an obviousness rejection, MPEP §2143.03 requires "all words of a claim to be considered" and MPEP §2141.02 requires consideration of the "[claimed] invention and prior art as a whole." Further, the Board of Patent Appeal and Interferences recently confirmed that a proper, post-KSR obviousness determination still requires the Office make "a searching comparison of the claimed invention - including all its limitations - with the teaching of the prior art." *In re Wada and Murphy*, Appeal 2007-3733, citing *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) and *CFMT v. Yieldup Intern. Corp.*, 349 F.3d

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1333, 1342 (Fed. Cir. 2003). In sum, it remains well-settled law that an obviousness rejection requires at least a suggestion of *all* of the claim elements.

In the paragraph spanning pages 10 and 11, the Office Action acknowledges:

Neither the '618 document, Strathdee or Bohl specifically teach inactivating the regulatable transcription factor so that expression of the reporter protein is decreased, incubation of the cell for a sufficient amount of time so that the cell goes through one or more cell cycles to generate a population of cells, detecting the amount of reporter in the population and then sorting the population of cells by the amount of reporter protein present in each cell, wherein sorted cells containing increased levels of the reporter is indicative of self-renewing, multipotent, slow cycling cells.

In an attempt to bolster this rejection, the Office Action goes on to assert:

However, prior to the time of filing, Mahmud et al. provide specific guidance to show that multipotent stem cells, such as hematopoietic stem cells, are considered slow-cycling cells (see Abstract). Additionally, the concept of separating rapidly dividing cells from slow-cycling cells is known in the art. For example, the '971 document discusses enrichment methods for keratinocyte stem cells, teaching that one may select a first population of cells from a partially enriched pool, and then provide a second enrichment step by separating cells with high and low binding levels from those which have low binding levels, using, for example antibodies and FACS techniques (col. 3, lines 49+-col. 4, lines 1-12, for example). Accordingly, Mahmud teach that pluripotent cells are slow-cycling, which would clearly maintain higher levels of reporter protein than cells that are dividing, and the '971 document provides clear guidance as to how to separate cells that have higher versus lower levels of protein expression (see the paragraph spanning pages 10 and 11).

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However, the above assertion as well as the remaining text of the rejections of record fail to identify where in the whole of the teachings of the cited references the active steps of instant claim 7 d)- 7 g) are found. A mere teaching of the use of antibodies, FACS techniques and sorting of slow-cycling cells from rapidly dividing cells does not constitute a teaching or suggestion of d) inactivating the regulatable transcription factor so that expression of the reporter protein is decreased; e) incubating the cell for a sufficient amount of time so that the cell goes through one or more cell cycles to generate a population of cells; f) detecting the amount of reporter protein in the population of cells; and g) sorting the population of cells by the amount of reporter protein present in each cell, as required by claim 7.

To support a conclusion that a claim is directed to obvious subject matter, prior art references must suggest expressly or impliedly the claimed invention or an Examiner must present a "convincing line of reasoning" as to why one of ordinary skill in the art would have found the claimed invention to have been obvious. *Ex parte Clapp*, 227 USPQ 972, 973 (BPAI 1985).

In the present case, the Office Action relied on the assertion that "[o]ne of skill in the art would be further motivated, in view of the teachings of Mahmud and the '971 document, to inactivate the regulatable transcription factor (by, for example, the withdrawal of doxycycline in the case of using the Tet system), and select for slow cycling stem cells by allowing the cells to divide, and selecting cells that contain a higher level of reporter protein expression." Page 9, ¶1 of the Office Action. However, Applicants

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respectfully assert that there is no factual basis or evidence of record to support the Examiner's conclusion. At most, the express disclosure of Mahmud fairly reads as teaching that subpopulations of bone marrow cells can be isolated by Hoechst/Rhodamine staining and CD34⁺ selection and that BrdU content of different subsets of cells is indicative of the replicative history of the cells. Likewise, the express disclosure of the '971 document fairly reads on a method of enriching for a viable subpopulation of epidermal cells having an altered proliferative potential compared with an unfractionated population of epidermal cells based upon a higher level of a cell surface integrin expression and expression of transerrin receptor, EGFR, IGFR or keratinocyte growth factor receptor. As such, the teachings of the references themselves lead the skilled artisan to conclude that surface markers and dye exclusion can be used to sort cells. There is simply no nexus to bridge the gap between the teachings of these references, in particular with that of the '618 document, Strathdee and Bohl. Without more, the cited references are only remotely related.

MPEP §2142 states that "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art." "Any judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is

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proper'" (MPEP §2145(X)(A), quoting *In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971).

Sorting of cells based upon cell cycle-mediated dilution or retention of a reporter protein is absent from the cited art and is only present in Applicants' Specification. Due to the lack of suggestion of steps 7 d) - 7 g) in the cited art of record and the fact that active steps 7 d) - 7 g) are only present on the record in Applicants' specification, it logically follows that the Examiner's conclusion has been improperly gleaned from Applicants' own specification and that the combination of US 5,639,618, Strathdee et al., Bohl et al., Mahmud and US 6,485,971, optionally in view of U.S. Patent No. 5,665,557, is an exercise of impermissible hindsight. Accordingly, it is respectfully submitted that the combination of cited references is improper and respectfully requested that the rejection be withdrawn.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record.

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Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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